

## UNIVERSITY OF ILLINOIS

May 9 1984

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Erick M. Carreira

ENTITLED An Approach to Hirsutene

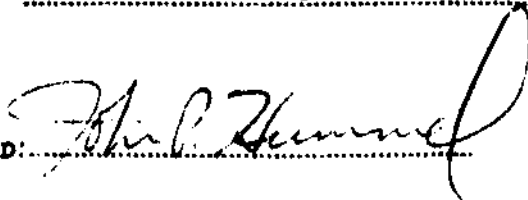
IS APPROVED BY ME AS FULFILLING THIS PART OF THE REQUIREMENTS FOR THE

DEGREE OF Bachelor of Science in Chemistry



Instructor in Charge

APPROVED:



HEAD OF DEPARTMENT OF Chemistry

AN APPROACH TO HIRSUTENE

BY

Erick Moran Carreira

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THESIS

For The  
Degree of Bachelor of Science  
In  
Chemistry

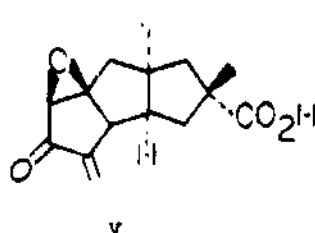
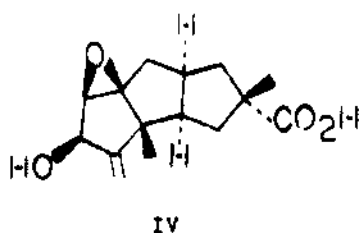
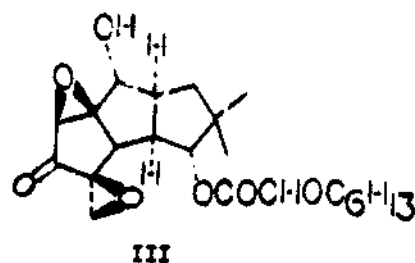
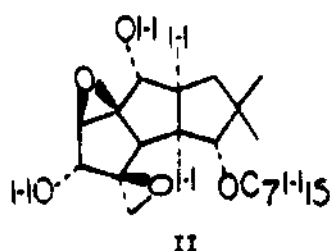
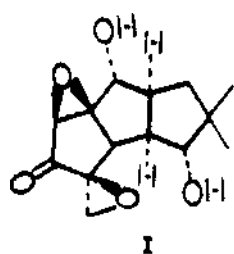
College of Liberal Arts and Sciences  
University of Illinois  
Urbana, Illinois  
1984

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## I. Introduction

Hirsutene has been implicated as the biogenetic precursor to the coriolins (I,II,III) isolated from Coriolus consors as well as to hirsutic acid (IV) and complicatic acid (V) isolated from Stereum hirsutum and Stereum complicatum respectively. These fungal sesquiterpenes have been shown to possess anti-tumor as well as antibacterial activity.<sup>1</sup>

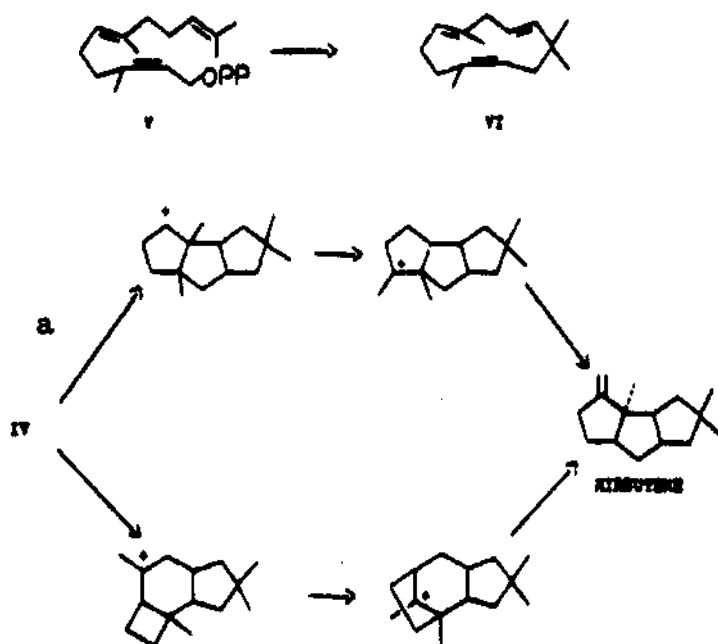


We became interested in hirsutene as a model for examining the penta-annulation method developed by Denmark.<sup>2</sup> In using the silicon-directed Nazarov cyclization we have been able to iteratively introduce suitably functionalized five-membered rings. The regio- and stereo-selectivity observed in these Lewis acid-catalyzed cyclizations is crucial, for it permits further synthetic transformations leading to the cis.

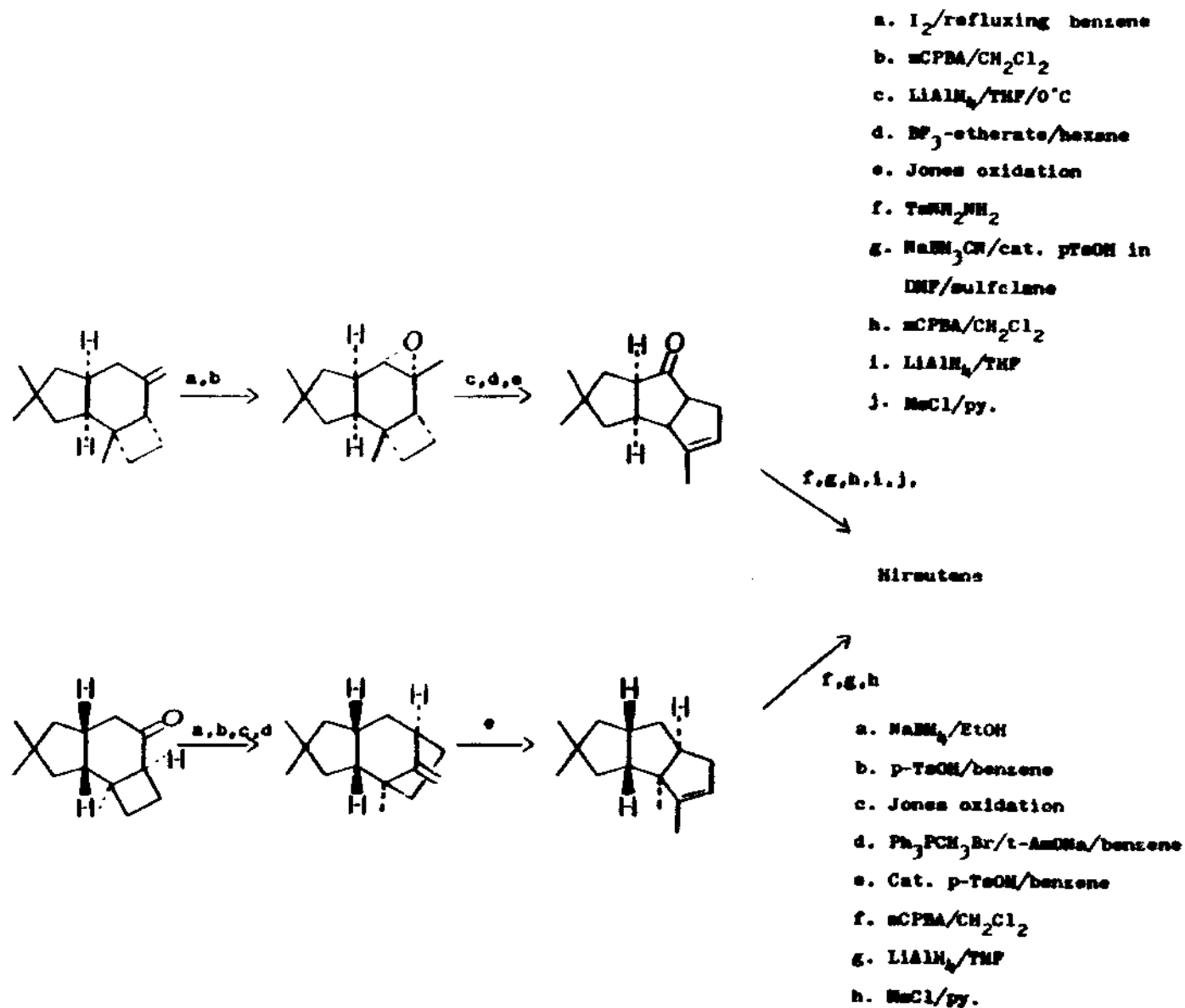
anti, cis-tricyclo [6.3.0.0<sup>2,6</sup>] undecane carbon skeleton of the hirsutane family.

The biosynthesis of the coriclines begins with the cyclization of farnesyl pyrophosphate (V) to humulene (VI). Tanabe<sup>3</sup> has concluded through FT-Carbon-13 spectral studies on the dihydrocoriolin C that the biosynthesis most likely proceeds through path a (see Scheme 1). However, another pathway proceeding through a protoilludyl cation has been suggested. Matsumoto<sup>4</sup> has shown that although attempted in vitro conversion of 7-protoilludanol to hirsutene has been unsuccessful, modified substrates such as  $\Delta^{7(13)}$ -protoilludene may be effectively converted. Nevertheless, Matsumoto has described two biogenetic-like transformations of both protoilludoids to hirsutene.<sup>4,5</sup> (Scheme 2)

Scheme 1

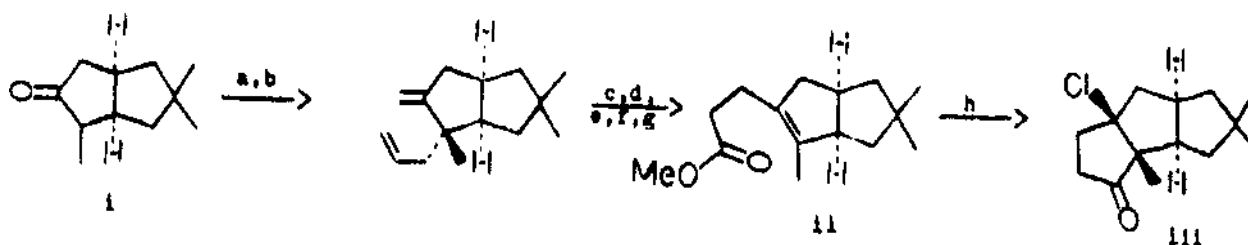


# Scheme 2



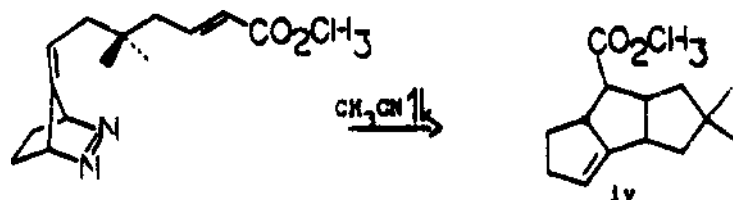
## II. Background

In the last eight years numerous synthetic approaches to hirsutene and other linearly fused cis,anti,cis-tricyclo [6.3.0.0<sup>2,6</sup>] undecanoid sesquiterpene natural products have been reported in the literature.<sup>6</sup> Nozoe<sup>7</sup> described in 1976 the first total synthesis of the fungal metabolite starting with the bicyclic ketone i whose synthesis had been previously reported by Matsumoto.<sup>8</sup> Nozoe introduces the necessary three-carbon unit for penta-annulation by alkylation of i, methylenation of the  $\gamma,\delta$  enone product followed by a Cope rearrangement. After several transformations he isolates ii and subsequently attaches ring A of the hirsutane skeleton using an intramolecular acylation of the tetra-substituted olefin giving a 20% yield of iii.

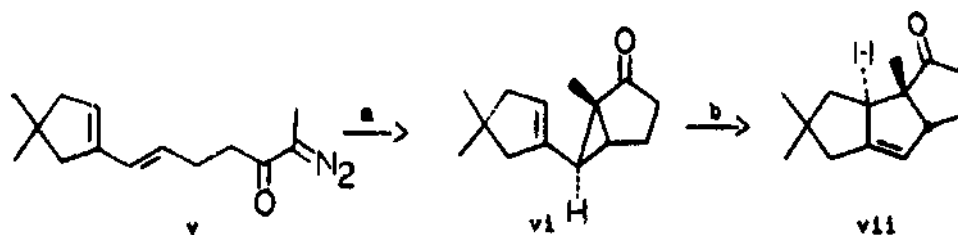


- a. NaH/DME, allyl chloride
- b. Ph<sub>3</sub>PCH<sub>2</sub>/DMSO
- c. 240°C
- d. OsO<sub>4</sub>/2:1 Et<sub>2</sub>O:pyr/ -78°C
- e. NaIO<sub>4</sub>/THF
- f. Ag<sub>2</sub>O-NaOH/aq. THF
- g. CH<sub>3</sub>OH (-H<sub>2</sub>O)
- h. C<sub>2</sub>O<sub>2</sub>Cl<sub>2</sub>/PhH tr. pyr./SnCl<sub>4</sub> in CS<sub>2</sub>

Little<sup>9</sup> has completed a total synthesis of hirsutene using an intramolecular 1,3-diyl trapping reaction which he developed in order to construct the linearly fused tricyclopentanoid ring system. In this key reaction Little simultaneously generates the B and C rings in a highly stereoselective fashion. The trapping proceeds in an 85% yield creating the necessary relative stereochemistry of the [6.3.0.0<sup>2,6</sup>] naturally occurring skeletons. His synthesis becomes rather lengthy in the subsequent manipulations of the C<sub>7</sub> methyl ester iv.



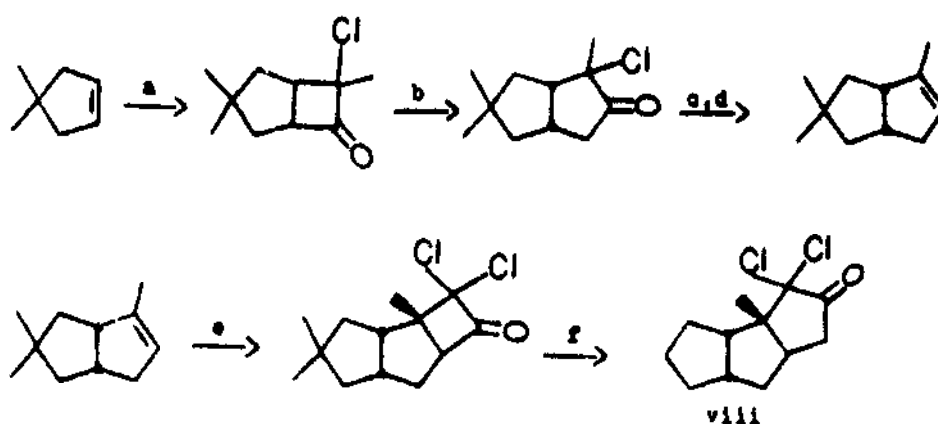
Hudlicky<sup>10</sup> provides an approach to hirsutene in which his key step involves construction of the A ring by an intramolecular cyclopropanation of dienic diazo ketone v to vi. This product subsequently gives rise to ring B by vinylcyclopropyl rearrangement to vii at elevated temperatures in the presence of lead carbonate.



- a. Cu(acac)<sub>2</sub>/benzene/
- b. 580°C/PbCO<sub>3</sub>/coated glass



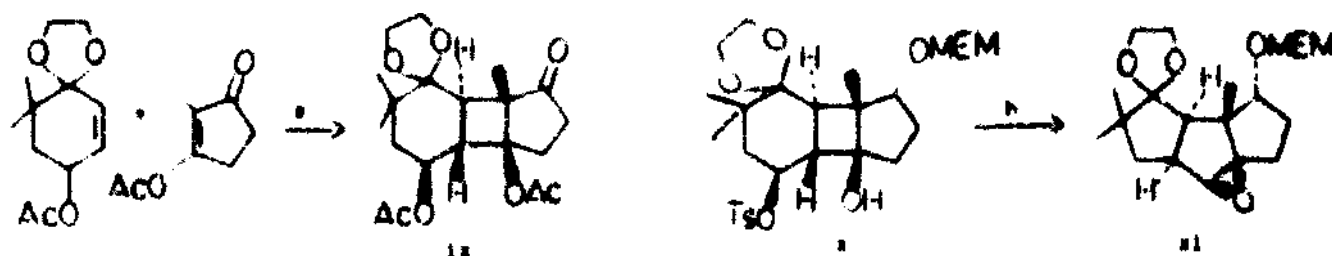
Greene<sup>11</sup> approaches the tricyclo undecanoid carbon skeleton by iteratively carrying out a [2+2] ketene cycloaddition followed by a Wolff rearrangement affording the ring expanded product viii. His three-carbon annelation method allows for a rather quick assembly of the linear triquinane system.



- a. methylchloroketene
- b.  $\text{CH}_2\text{N}_2$
- c.  $\text{NaBH}_4$
- d.  $\text{Cr}(\text{ClO}_4)_2$
- e. dichloroketene
- f.  $\text{CH}_2\text{N}_2$

Tatsuda<sup>12</sup> has reported a stereocontrolled synthesis of hirsutene as a general method of entry into the cis,anti,cis-undecane series. His crucial step is the skeletal rearrangement of a 6-4-5 fused ring system to a 5-5-5 fused system. Tatsuda utilizes the [2+2] photocycloaddition developed by de Mayo in arriving at ix. After a reduction and a series of

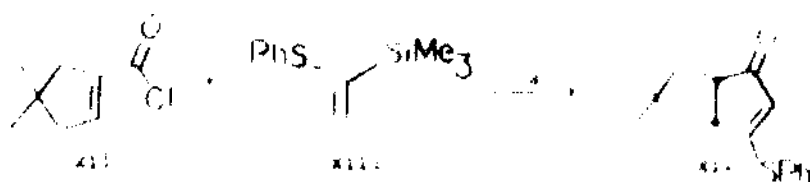
manipulations he induces the rearrangement of x to xi.

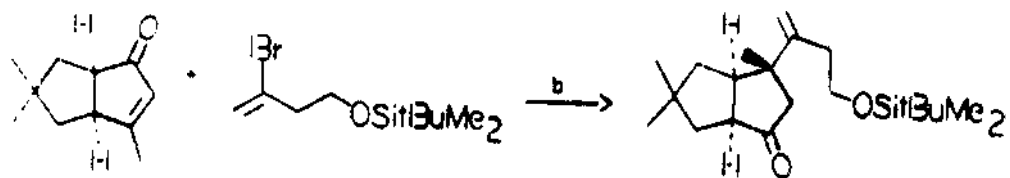


- a. 400-W mercury lamp/60 hr. 20°C  
b.  $K_2CO_3$ /60% acetone/85°C 1 day

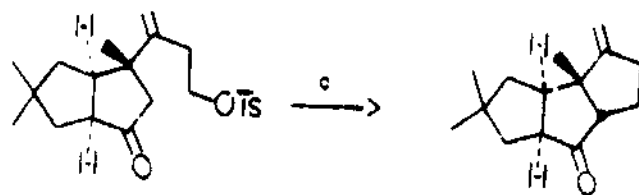
In a recent communication dealing with silicon in organic synthesis, Magnus describes a silicon-mediated penta-annulation method.<sup>13</sup> Magnus appends the B ring onto cyclopentenoyl chloride xii by treatment with 1-(trimethylsilyl)-1-(phenylthio)ethylene (xiii) in the presence of silver tetrafluoroborate.

This transformation does provide a short synthesis of the [3.3.0] bicyclooctanoid precursor xiv. However, the penta-annulation possesses two disadvantages in that it only proceeds in modest yield (38%), and is not used in the following steps to introduce the A ring of the natural product, thereby leaving the carbon skeleton.

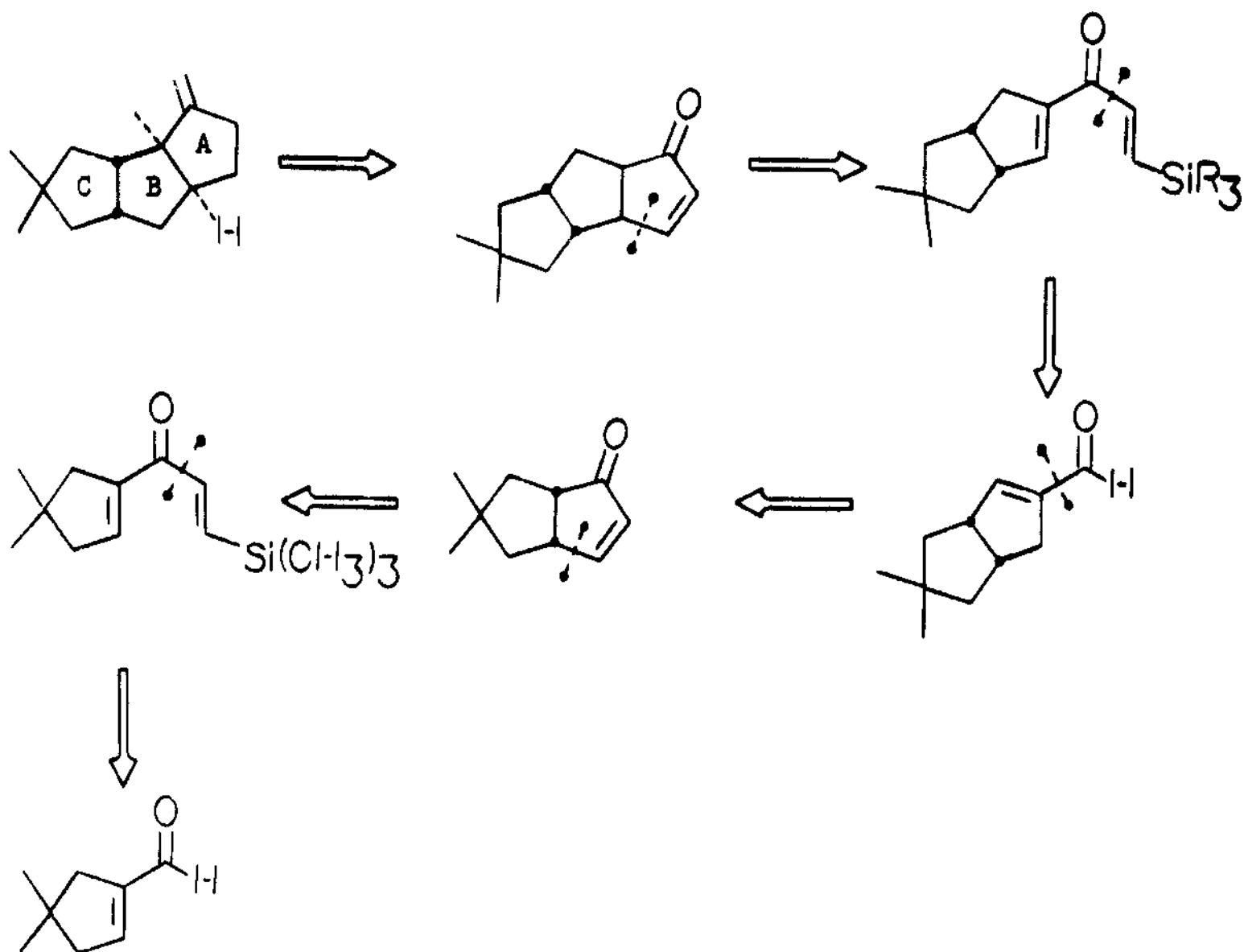




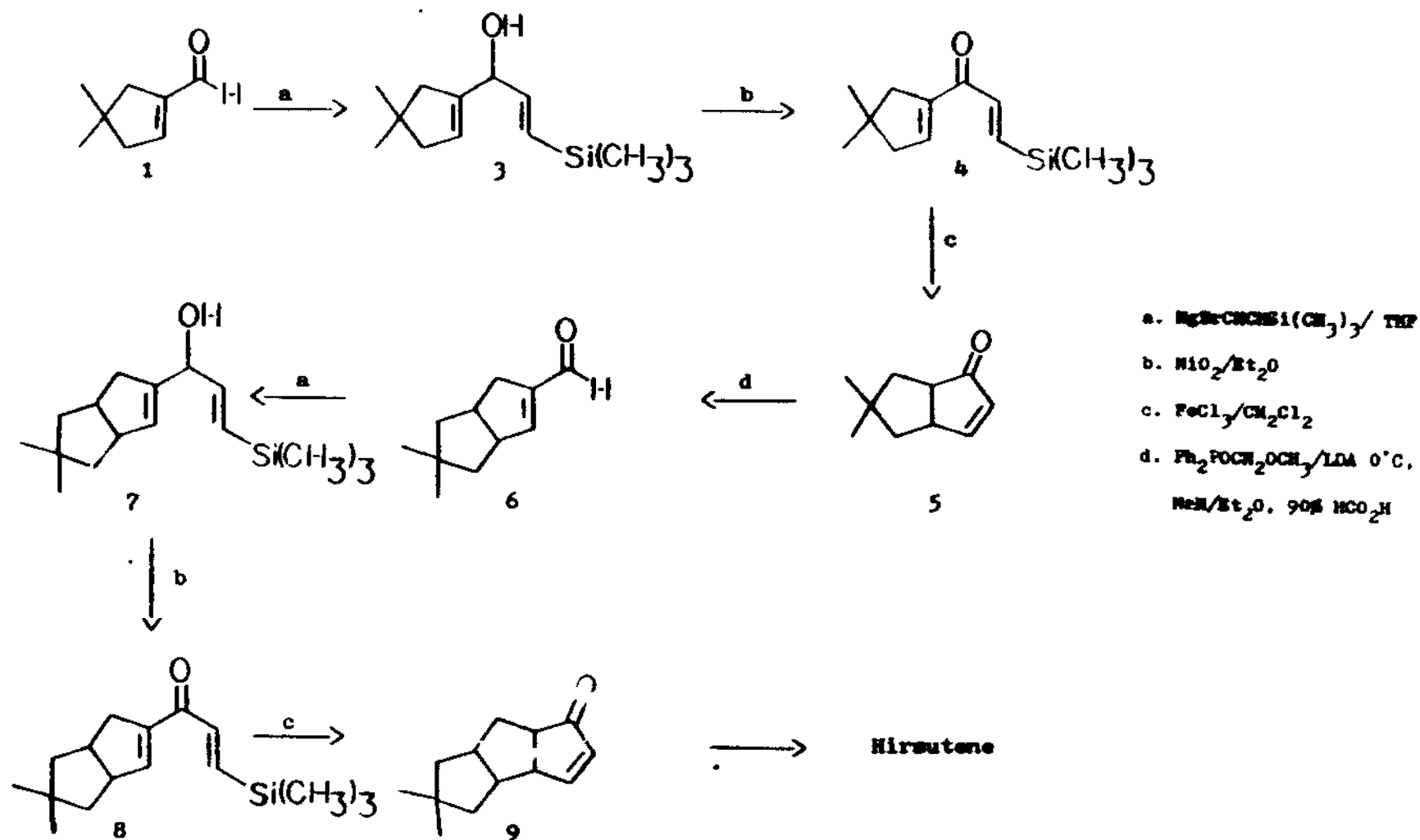
- a. AgBF<sub>4</sub>/CH<sub>2</sub>Cl<sub>2</sub> -20°C
- b. tBuLi/Et<sub>2</sub>O/ -100°C/CuCl
- c. Lithiohexamethyldisilazane/Et<sub>2</sub>O/ -78°C



Retro-synthetic Analysis



# Synthetic Scheme



### III. Results and Discussion

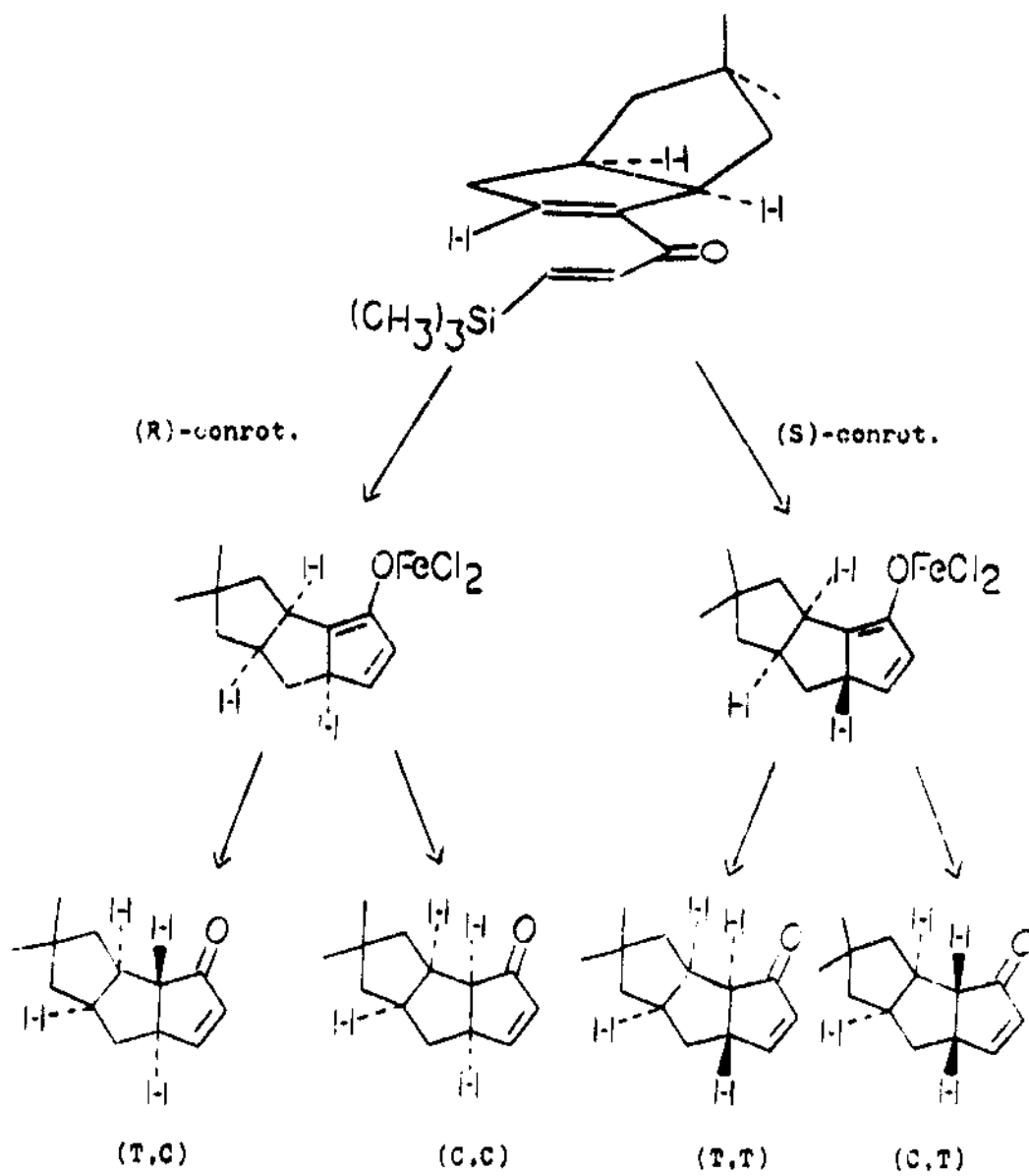
Our synthetic strategy begins with 4,4-dimethylcyclopentene-1-carboxaldehyde 1, a rather popular starting material in the field of coriolin and illudane synthesis. The synthesis of 1 is easily accomplished in five steps from dimedone. The crucial ring contraction is effected in toluene using a lithium bromide-hexamethylphosphoric triamide (HMPA) complex catalytically as described by Magnusson and Thoren.<sup>14</sup> The cyclopentenylaldehyde 1 is treated with the vinyl Grignard 2 affording in 96% yield diallyl alcohol 3. This dienol can be chromatographed on  $\alpha$ silica gel and should be purified for best results in the oxidation that follows. A mixture of cis and trans silyl olefins are obtained which reflect the ratio of isomers in the (E)-(2-bromoethenyl)trimethylsilane.

Diallyl alcohol 3 is subsequently treated with  $\text{NiO}_2$  in anhydrous ether giving in 75% yield dienone 4. It is interesting to note that in this transformation the mixture of cis and trans olefins from the previous step gives rise to a single isomeric dienenone. Kugelrohr distillation of 4 affords a crystalline compound which is subsequently treated with 1.05 eq. of  $\text{FeCl}_3$  in methylene chloride to give in 83% yield cyclopentenone 5. Careful scrutiny of the NMR spectrum reveals the presence of isomers which when heated converge to the desired bicyclo [3.3.0] enone. In spite of the fact that both of the isomers observed are separable on  $\alpha$ silica

gel, all attempts at isolation of what apparently is the trans-fused system failed.

We must next convert 5 to its aldehyde homolog in order to introduce the A ring of the illudane skeleton. This was effected using the procedure devised by Warren.<sup>15</sup> Enal 6 was subjected to the Grignard addition and oxidation steps described previously to give 8. We were expecting the Lewis acid-catalyzed closure of 8 to the tricyclic product to proceed in a highly stereoselective fashion resulting in the cis, anti, cis- [6.3.0.0<sup>2,6</sup>] hirsutane skeleton; however, to our own amazement, the silicon-directed Nazarov cyclization gave a 3.9:1 (GC) mixture of isomers. The results of the first cyclization lead us to question the identity of the two isomers observed. In order to systematize the description of possible isomers involved, a nomenclature involving two descriptors cis (C) or trans (T) is employed.<sup>2</sup> The first descriptor in a given pair defines the A-B ring fusion stereochemistry and the second defines the relationship between the H-atom at 4' and the H-atom at 3' (Scheme 3). The sense of conrotation sets up the stereochemistry at the 3' angular position and defines a stereochemical family. Subsequent protonation at 1' determines the ratio of isomers within a given family. The simplest way of determining the nature of the products is to follow the approach used by Denmark and Jones. Catalytic hydrogenation of the mixture gave a new mixture of saturated ketones whose relative composition was

Scheme 3





identical to that of the enone. Note that by removing the unsaturation, the two isomers are locked into their configurational families. Base catalyzed epimerization should only change the relative amounts of the two components if the two isomers differ only in ring fusion; but, in all other cases, epimerization should produce new isomers at the expense of the original ones. In the experiment, no change was observed in the composition of isomers after treatment with base. We thus concluded that the mixture consisted of cis-syn-cis (C,C) and cis-anti-cis (C,T) isomers.

We subsequently decided to allow silicon even greater power in control of the annelation by substituting isopropyl for methyl in the  $\beta$ -silyl-substituted divinyl ketone. However, failure to be able to prepare (E)-2-(Triisopropylsilylethenyl)-tributylstannane<sup>2</sup> as well as lack of time made this option unattainable.

## Experimental Section

### General Experimental Information

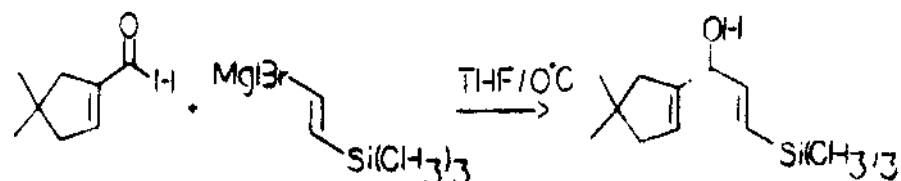
$^1\text{H}$  NMR spectra were recorded on a Nicolet NTC-360 (360MHz) spectrometers in deuteriochloroform with chloroform as an internal standard ( $\delta$  7.26) unless otherwise stated. Chemical shifts are given in ppm( $\delta$ ); multiplicities are indicated by s(singlet), d(doublet), t(triplet), q(quadruplet), m(multiplet), or br(broadened). Infrared spectra were obtained on Perkin Elmer 1320 spectrophotometer. Peaks are reported in  $\text{cm}^{-1}$  with the following relative intensities: s(strong, 67-100%), m(medium, 34-66%), w(weak, 0-33%). Mass spectra were obtained on a Varian MAT CH-5 spectrometer with ionization voltages of 10 and 70eV. Data are reported in the form of m/e (intensity relative to base=100). Elemental analyses were performed by the University of Illinois Microanalytical Service Laboratory. Bulb to bulb distillations were performed in a Euchi GKR-50 Kugelrohr; boiling points refer to air bath temperatures and are uncorrected. Analytical TLC was performed on Merck silica gel plates with QF-254 indicator. Visualization was accomplished with UV light, phosphomolybdic acid, iodine, and/or vanillin. Solvents for extraction and chromatography were technical grade and distilled from the following drying agents: hexane ( $\text{CaCl}_2$ ); ether ( $\text{CaSO}_4/\text{FeSO}_4$ ); ethyl acetate ( $\text{K}_2\text{CO}_3$ ). Analytical gas chromatography was performed on a Varian 3700 chromatograph fitted with a flame ionization detector. ( $\text{N}_2$  carrier gas for packed columns

(30 mL/min),  $H_2$  for capillary columns (1 mL/min). Columns:  
A- 50m capillary OV-17, split ratio 30:1; B- 12 ft. 5% OV-17  
on 60-80 acid washed chromosorb G. Retention times and  
integrals were obtained from a Hewlett Packard 3390 recorder.  
nButyllithium was titrated according to the method of Gilman.<sup>16</sup>  
Nickel peroxide was prepared and titrated as described by  
Nakata and co-workers.<sup>17</sup> All reactions were performed in oven  
of flame dried glassware under an atmosphere of dry  $N_2$ .

Reagents, Suppliers, and Purification

Acetone	Fischer, distilled
nButyllithium	Aldrich
Bromine	Fischer Scientific
Calcium Hydride	Alfa
1,2-Dichloroethane	Mallinckrodt, passed through $\text{Al}_2\text{O}_3$
Dichloromethane	MCB, distilled from $\text{CaH}_2$
Diethyl ether	J.T. Baker, distilled from Na/benzophenone
Ethyl acetate	Fischer, distilled from $\text{K}_2\text{CO}_3$
Ferric chloride	Aldrich
Formic Acid, 90%	MCB
Hexane	Burdick and Jackson, distilled from $\text{CaCl}_2$
Iodine	Mallinckrodt
Magnesium chips/resublimed	Alfa
Nickel sulfate, hexahydrate	J.T. Baker
Potassium Carbonate	Mallinckrodt
Sodium	Alfa
Sodium Chloride	Mallinckrodt
Sodium Hydride	Alfa
Tetrahydrofuran	Aldrich, distilled
Tri-nbutyltin hydride	Aldrich
Triisopropylsilyl chloride	Aldrich
Trimethylsilyl chloride	Silar
Vanillin	Aldrich
Vinyltrichlorosilane	Petrarch

Reaction of 1 with (E)-(2-bromoethenyl)trimethylsilane



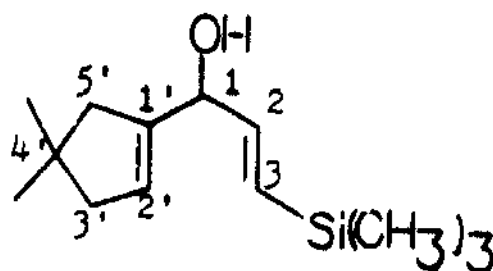
A three-necked 500mL flask fitted with an addition funnel, magnetic stirrer, thermometer, and nitrogen inlet is charged with 5.64g (0.232 mol) of resublimed magnesium chips and 20.0mL of THF. A solution of 34.62g (0.193 mol) (E)-(2-bromoethenyl)trimethylsilane<sup>18</sup> in 87.7mL of dry THF is added dropwise with vigorous stirring over 1.25 hr. After complete addition the yellow-green mixture is stirred for an additional two hours at room temperature.

The yellow-green suspension is cooled to -5°C using an ice/salt/water bath and a solution of 16.0 g (0.129 mol) of the enal 2<sup>14</sup> in dry THF is added dropwise through an addition funnel for 1 hr. The resulting colorless mixture is stirred for 15 minutes and subsequently checked by TLC.

The reaction mixture is quenched with 200mL of a 4% NH<sub>4</sub>Cl solution at 0°C. The reaction mixture is poured into a separatory funnel and the layers separated. The aqueous phase is extracted with ether (3x150mL). The combined ethereal solutions are washed once with 150mL of water and brine, dried over K<sub>2</sub>CO<sub>3</sub> for 20 minutes, and concentrated to afford a quantitative yield of product. The crude diallyl alcohol is chromato-

graphed on Woelm (32-63) yielding 27.74g (96%) of chromatographically homogeneous 3.

Analytical Data from 3



M.W.: 224.46

b.p.: 100°C 3 torr Kugelrohr

<u>C<sub>13</sub>H<sub>24</sub>OSi:</u>	calc.:	C 69.58%	H 10.78%
	found:	C 69.71%	H 10.90%

<sup>1</sup>H NMR: (360 MHz, CDCl<sub>3</sub>)

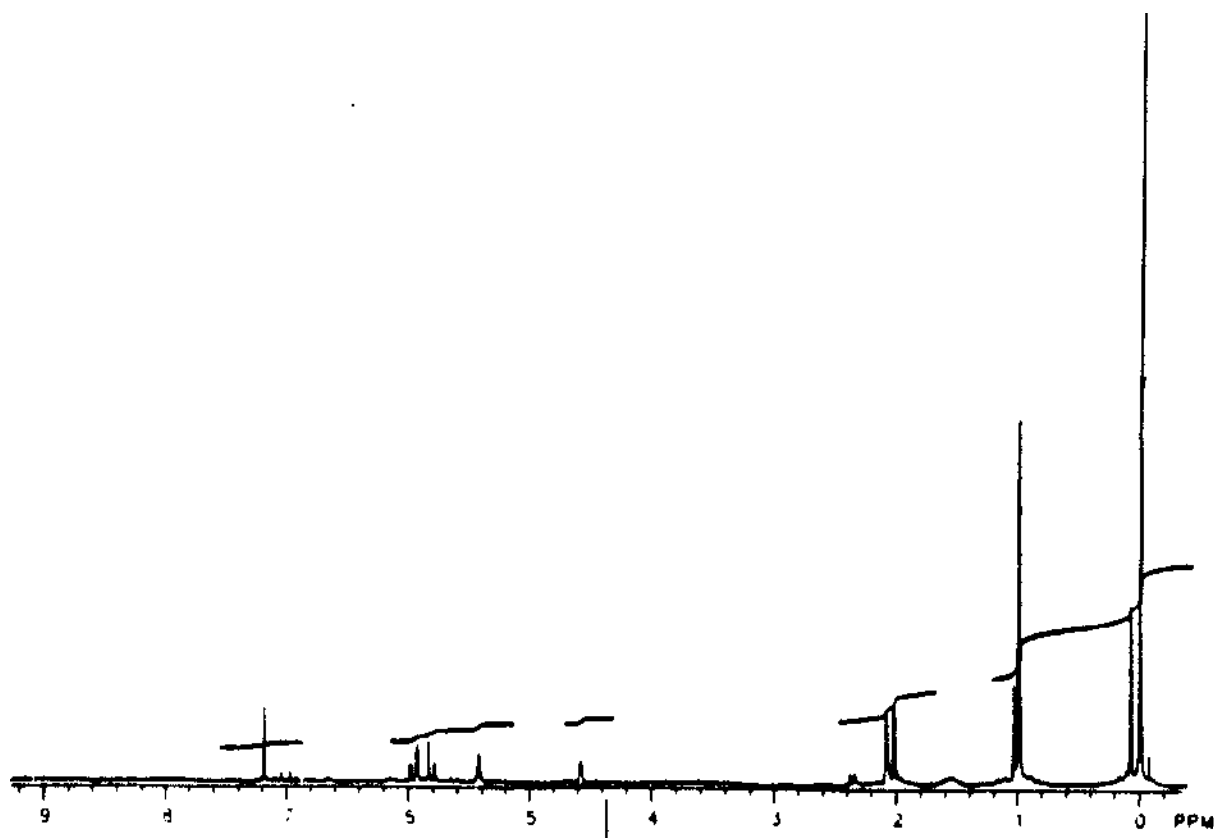
6.15 (d, J=18.4Hz, 1H, H-C(2)(Z)); 7.03 (d, J=18.7Hz, 1H, H-C(3)(Z));  
 6.75 (m, 1H, H-C(2')(E)); 6.05 (dxd, J=18.7Hz and J=5.2Hz, 1H, H-C(2)(E));  
 5.90 (dxd, J=18.7Hz and J=0.9Hz, 1H, H-C(3)(E)); 5.51 (m, 1H, H-C(2')(Z));  
 4.67 (m, 1H, H-C(1)(Z)); 2.47-2.42 (m, 4H, 2H-C(3') and 2H-C(5')(E));  
 2.17-2.11 (m, 4H, 2H-C(3') and 2H-C(5')(Z)); 1.72-1.59 (br m, 1H, OH(Z));  
 1.13 (s, 6H, 2CH<sub>3</sub>-C(4')(E)); 1.092 (s, 3H, 1CH<sub>3</sub>-C(4')(Z)); 1.086 (s,  
 3H, 1CH<sub>3</sub>-C(4')(Z)); 0.16 (s, 9H, (CH<sub>3</sub>)<sub>3</sub>Si(E)); 0.09 (s, 9H, (CH<sub>3</sub>)<sub>3</sub>Si(Z)).

MS: (70eV)

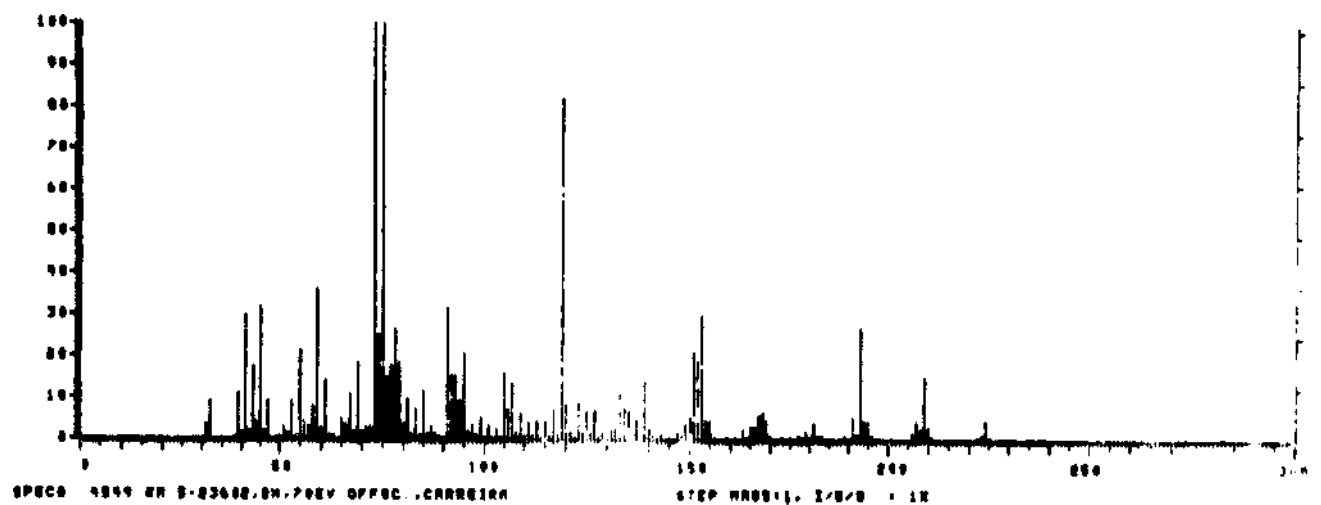
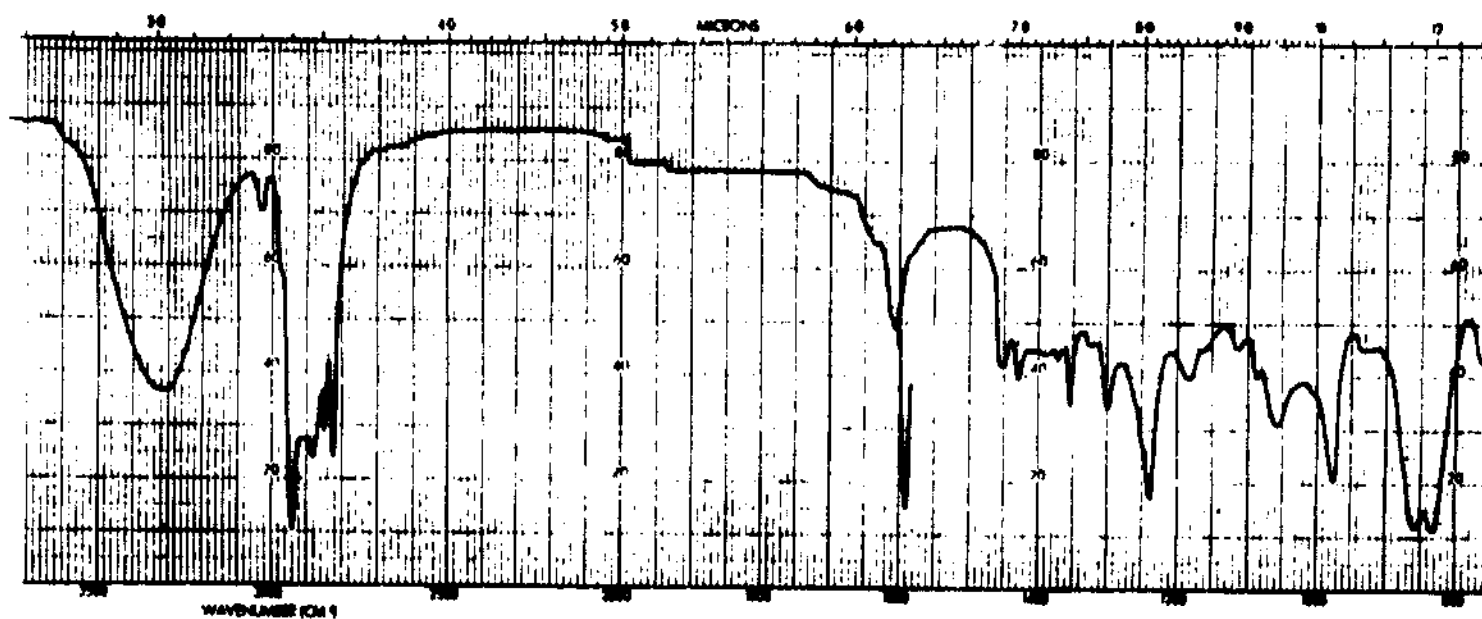
224 ( $M^+$ , 4.33), 209 (11.92), 193 (18.59), 153 (18.67), 152 (14.25),  
151 (16.35), 119 (51.05), 95 (10.71), 92 (10.89), 78 (13.25),  
75 (66.28), 73 (100).

IR: (Neat)

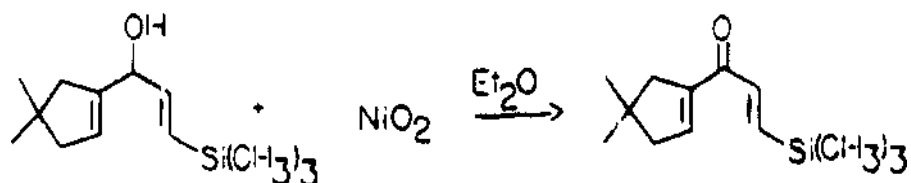
3320m (br), 3050w, 2960s, 2900s, 2880s, 2850s, 1615m, 1465m,  
1440m, 1365m, 1310m, 1250s, 1190m, 1125m, 1095m, 1065m, 985s,  
870s, 840s, 775m, 750s, 735m, 695m.





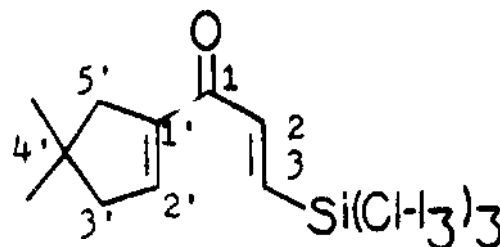


Oxidation of 3 with Nickel Peroxide



A dry, three-necked, 1L flask equipped with a thermometer, mechanical stirrer, and nitrogen inlet is charged with 153mL of anhydrous ether and 27.38g (0.122 mol) of the diallyl alcohol. The solution is cooled to 0°C, and 83.71g (2.1 eq) of NiO<sub>2</sub> is added in one portion through a powder funnel. The dark suspension is stirred at 0°C for 10 minutes and then allowed to come to room temperature. The heterogeneous mixture is allowed to react at room temperature for 2.5 hr. The contents of the reaction vessel are filtered through a Büchner funnel and the NiO<sub>2</sub> washed thoroughly with reagent grade acetone. The filtrate is concentrated on a rotary evaporator to yield 21.57g (80%) of a light yellow solid. The solid product is purified by Kugelrohr distillation at reduced pressure.

Analytical Data from 4



M.W.: 222.44

b.p.: 110°C at 3 torr Kugelrohr

C<sub>13</sub>H<sub>22</sub>OSi      calc.: C 70.21%    H 9.97%  
                      found: C 70.07%    H 9.95%

<sup>1</sup>H NMR: (360 MHz, CDCl<sub>3</sub>)

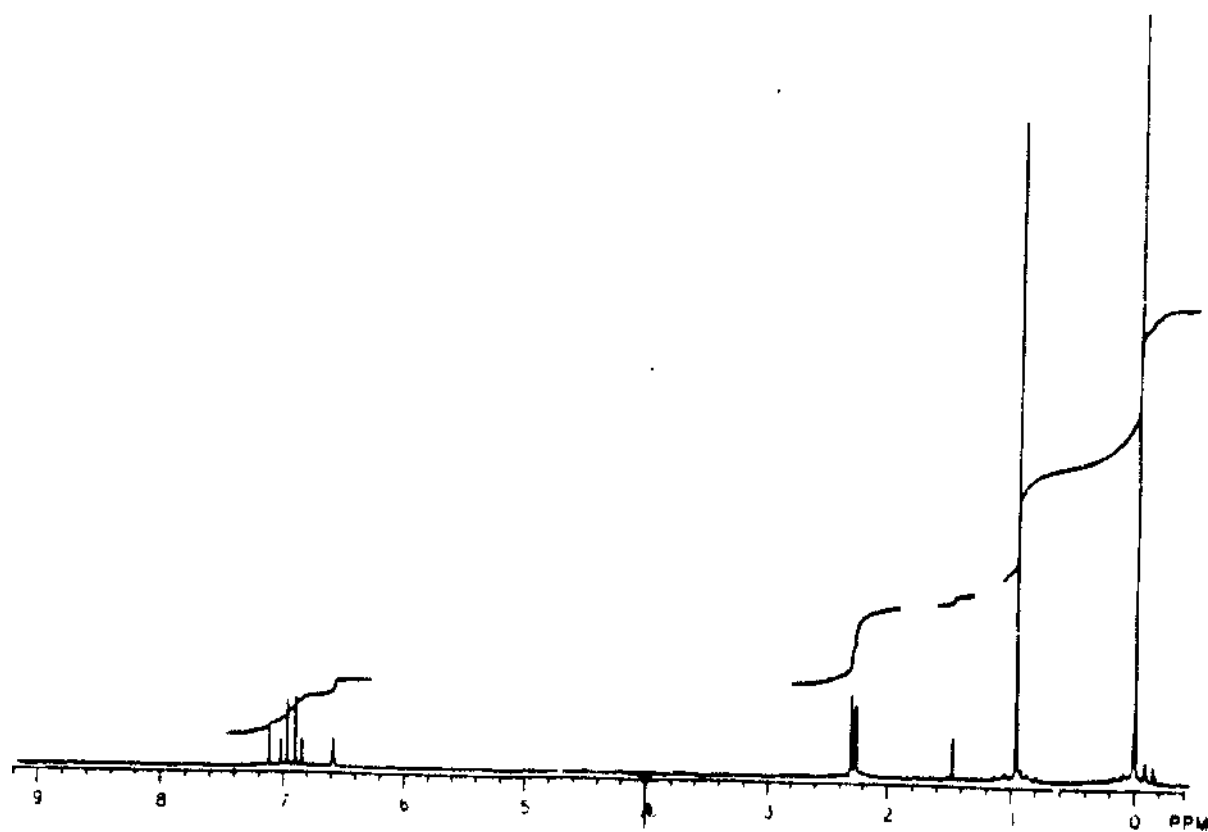
7.15 (d, J=18.7Hz, 1H, H-C(2)); 7.03 (d, J=18.6Hz, 1H, H-C(3));  
 6.75 (m, 2H, H-C(2')); 2.47-2.41 (m, 4H, 2H-C(3') and 2H-C(5'));  
 1.64 (s, 6H, 2CH<sub>3</sub>-C(4')); 0.16 (s, 9H, (CH<sub>3</sub>)<sub>3</sub>Si).

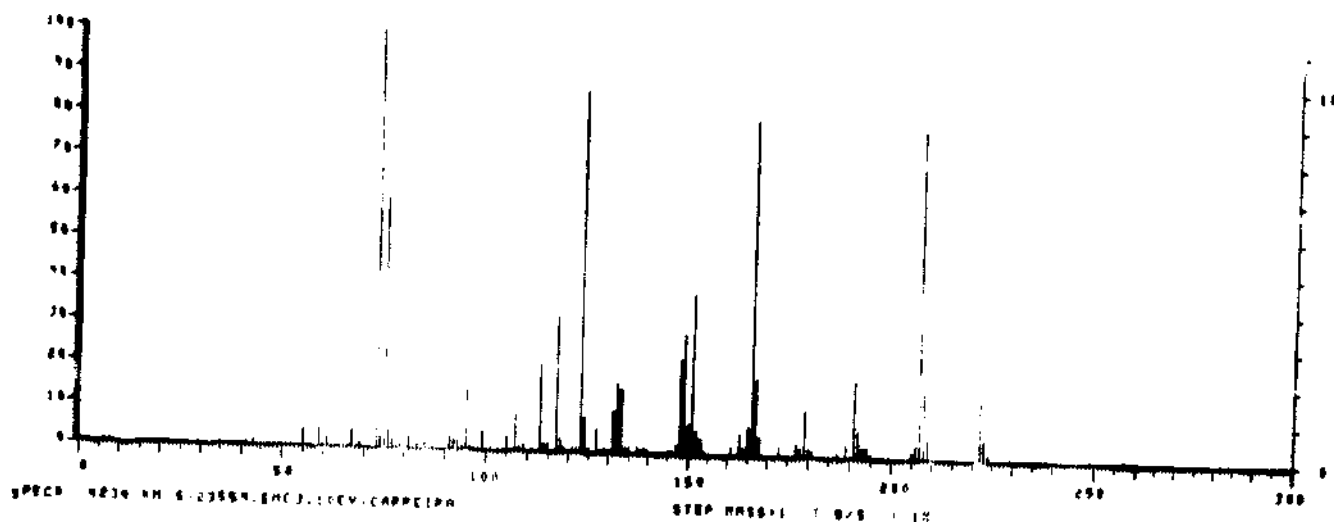
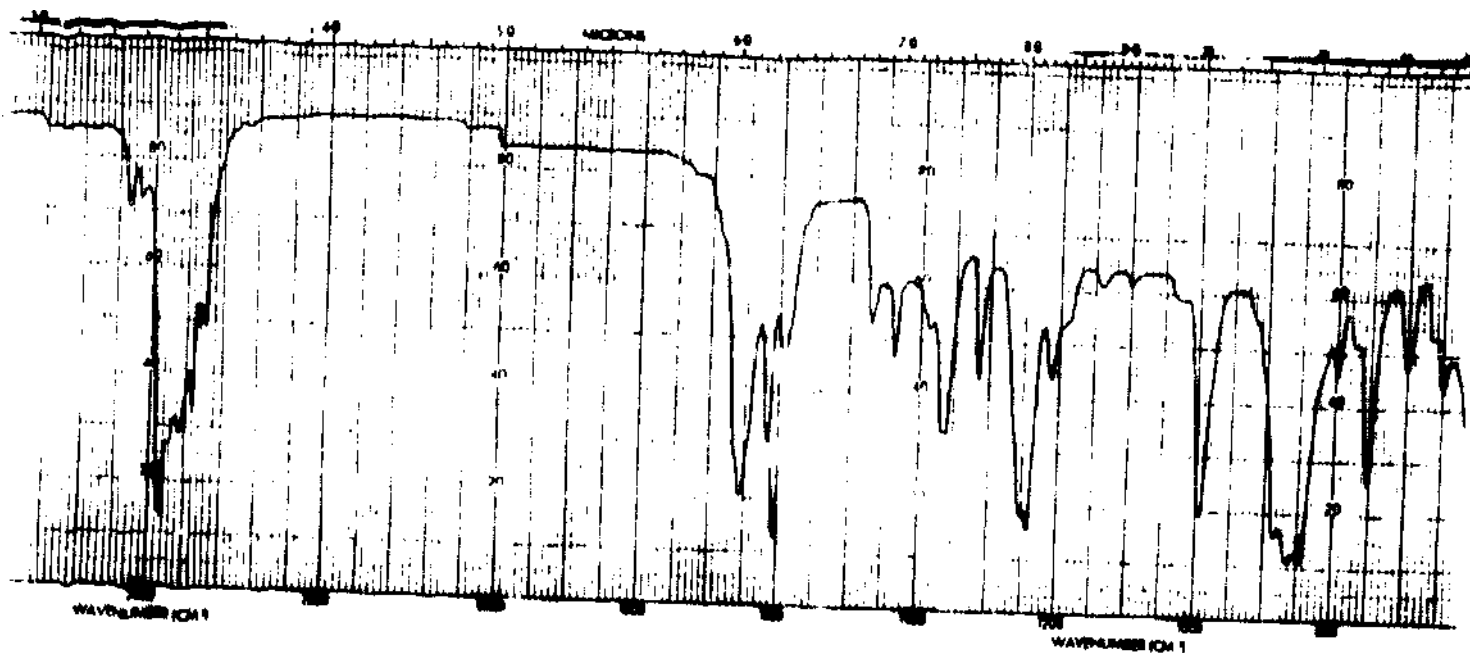
IR (Neat)

3060w, 2950s, 2900s, 2870s, 2850m, 2830m, 1625s, 1610s, 1585m,  
 1465m, 1430m, 1385m, 1360m, 1320m, 1245s, 1235s, 1205m, 1135w,  
 1095w, 990s, 875s, 855s, 840s, 795w, 745m, 695w, 645w.

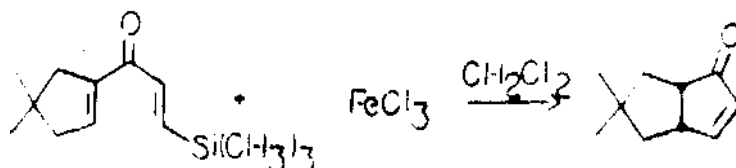
MS : (70eV)

222 ( $M^+$ , 18.6), 208 (16.2), 207 (79.0), 191 (18.6), 179 (11.3),  
167 (19.0), 166 (80.7), 151 (38.4), 149 (28.8), 148 (22.8),  
133 (15.6), 132 (16.7), 131 (10.3), 123 (87.2), 117 (32.5),  
113 (21.3), 95.1 (14.3), 75 (60.3), 73.1 (100).





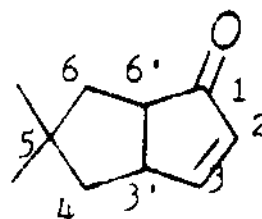
The Silicon-directed Nazarov Cyclization of 4



A 1-L flask equipped with  $\text{CaCl}_2$  drying tube and magnetic stirrer is charged with 9.83g (0.0442 mol) of the dieneone in 450mL of methylene chloride. To the vigorously stirred solution is added 7.53g (1.05 eq) of  $\text{FeCl}_3$  in one portion and the reaction progress is monitored by TLC. After 2.5 hr. the reaction is judged complete and the contents of the flask poured into a separatory funnel. The dark-orange organic solution is washed repeatedly with brine until the brine wash is colorless. The brine washes are back extracted twice with 200mL of ether. The combined organic solutions are washed once with 200mL brine, dried over  $\text{MgSO}_4$ , and concentrated on a rotary evaporator. The product is immediately chromatographed on a silica gel using 3:1 hexane:ethyl acetate as the solvent system. A second chromatography may be needed in order to effectively remove the iron impurities. Isolation of the fractions immediately preceding the fractions known to contain the desired product yielded a compound identical by NMR to the desired product. Therefore, it can only be concluded that

isomerization to the cis-fused enone occurred at some point in the isolation process. The final yield of the bicyclo enone is 5.48g (83%).

Analytical Data for 5



M.W.: 150.22

b.p.: 90°C 7 torr Kugelrohr

C<sub>10</sub>H<sub>14</sub>O: calc.: C 79.96% H 9.39%  
found: C 79.82% H 9.52%

<sup>1</sup>H NMR: (360 MHz, CDCl<sub>3</sub>)

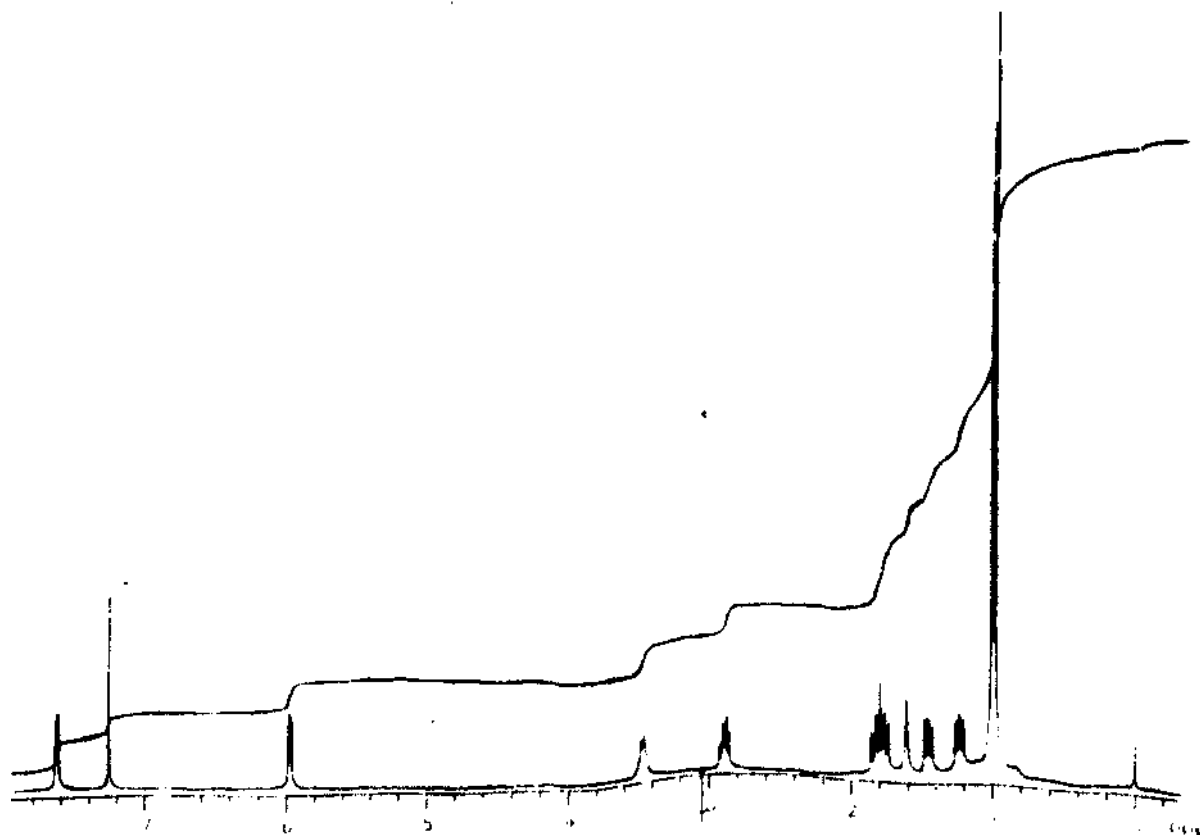
7.64 (dx1, J=2.8Hz and J=5.5Hz, 1H, H-C(1)); 5.99 (ixd, J=1.8Hz and J=5.6Hz, 1H, H-C(2)); 3.51-3.45 (br m, 1H, H-C(3')); 2.91 (dx dx d, J=9.8Hz, J=6.5Hz, and J=2.2Hz, 1H, H-C(6')); 1.84-1.62 (m, 2H, H-C(6) and H-C(4)); 1.49-1.44 (m, 1H, H-C(6)); 1.27-1.21 (m, 1H, H-C(4)); 1.03 (s, 3H, 1CH<sub>3</sub>-C(5)); 1.00 (s, 3H, 1CH<sub>3</sub>-C(5)).

M.S.: (70eV)

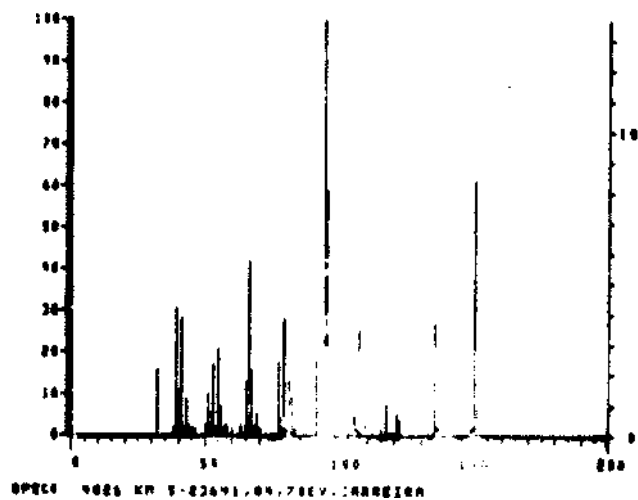
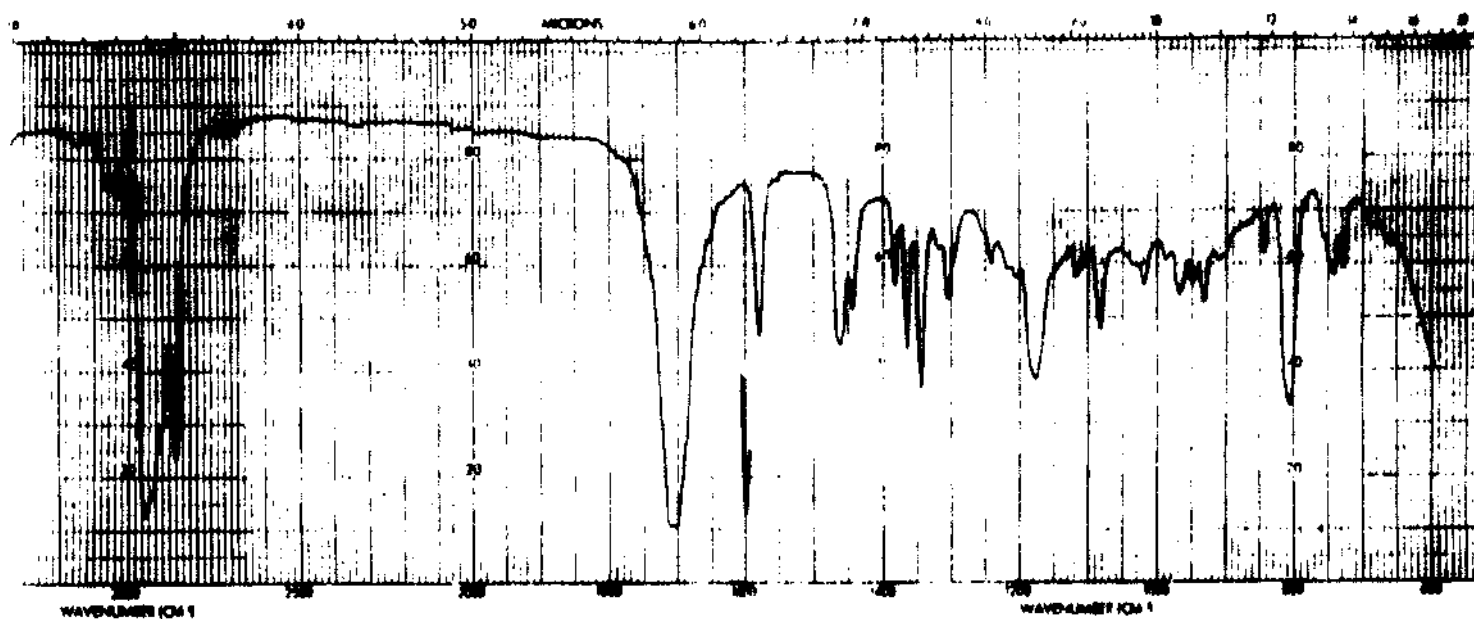
150 ( $M^+$ , 61.40), 135 (27.89), 108 (15.41), 107 (25.53), 95 (59.14),  
94 (100), 93 (15.41), 91 (18.00), 82 (10.01), 81 (13.56), 79 (28.36),  
77 (17.93), 67 (15.82), 66 (42.01), 65 (13.32), 55 (21.22),  
53 (17.02), 51 (10.34), 41 (28.41), 40 (10.73), 39 (30.96).

IR: (Neat)

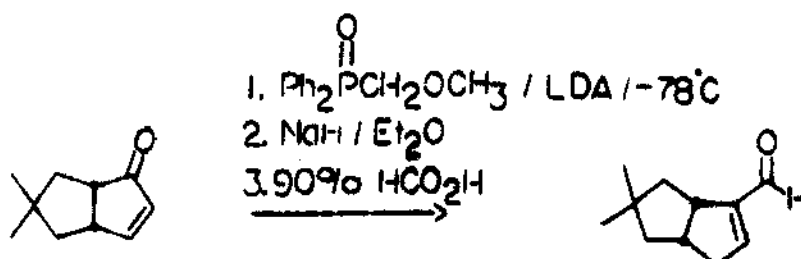
3070w, 3040w, 2950s, 2930s (sh), 2900s (sh), 2860s, 1705s, 1580m,  
1465m, 1445m, 1385m, 1365m, 1345s, 1305m, 1245m, 1180m, 1120m,  
1085m, 1020m, 970m, 950m, 935m, 845w, 805s, 750m (sh), 745m, 730m.







Homologation of 5



Methods

In a 1-L flask equipped with mechanical stirrer, nitrogen inlet, addition funnel and thermometer is placed 6.27mL (1.15 eq) of diisopropyl amine in 60.0mL of THF. The solution is cooled to  $0^\circ\text{C}$  using an ice-water bath. To the cold vigorously stirred solution is added 28.2mL (1.1 eq) of a 1.52 M solution of nBuLi in hexane over a 15 minute interval.

The cold, vigorously stirred LDA solution is treated with 10.53g (1.1 eq) of the phosphine oxide in 100mL of THF. The orange anionic solution is subsequently cooled to  $-78^\circ\text{C}$  using an isopropyl alcohol-dry ice bath. To the cold solution is slowly added 5.84g (0.0389 moles) of the enone in 180mL of THF over 1.5 hours. After complete addition the reaction mixture is stirred at  $-78^\circ\text{C}$  for an additional 10 minutes.

The reaction mixture is quenched by the cautious addition of 250mL of a 4%  $\text{NH}_4\text{Cl}$  solution and allowed to come to room temperature. The contents of the reaction vessel are poured into a separatory funnel and the layers separated. The aqueous layer is extracted three times

with 150mL of ether and the combined ethereal layers washed once with 100mL of brine. The ethereal solution is dried over  $\text{MgSO}_4$  for 30 minutes, filtered, and concentrated on a rotary evaporator.

A 250mL flask equipped with thermometer, magnetic stirrer, nitrogen inlet, and addition funnel is charged with 1.21g (1.5 eq) of NaH in 30mL of THF. The resulting suspension is cooled to 0°C using an ice/salt/water bath and subsequently treated with a solution of the crude product from the previous step in 50mL of THF. After complete addition the bath is removed and the brown suspension allowed to stir overnight at room temperature.

The reaction mixture is quenched with 200mL of a 4%  $\text{NH}_4\text{Cl}$  solution. The two phase mixture is poured into a separatory funnel and the layers separated. The aqueous phase is extracted three times with 100mL of ether and combined ethereal solutions washed once with 50mL of brine. The solution is dried over  $\text{MgSO}_4$  for twenty minutes, filtered, and concentrated on a rotary evaporator.

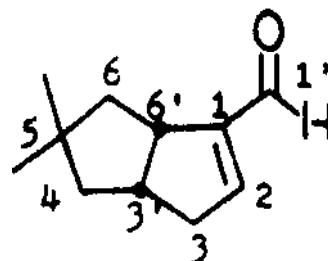
A 250mL flask equipped with magnetic stirrer is charged with the crude enol ether and 70mL of 90% formic acid. The resulting solution is stirred for 3.5 hr. and checked by TLC.

The reaction mixture is diluted with 350mL of ether and subsequently extracted four times with 100mL of water. The combined aqueous washes are made basic using a 15% NaOH solution. The ethereal solution is cautiously washed five times with 50mL portions of a saturated  $\text{NaHCO}_3$  solution. The combined alkaline aqueous washes are back-extracted four times with 100mL of ether. The combined organic phases are washed once with 100mL brine, dried over  $\text{MgSO}_4$  for twenty

minutes, filtered, and concentrated on a rotary evaporator to give a thick orange oil.

The crude product is purified by flash chromatography on silica gel using 7:1 hexane:ethyl acetate as the solvent system to give 2.34g (37%) of the desired enal.

Analytical Data from 6



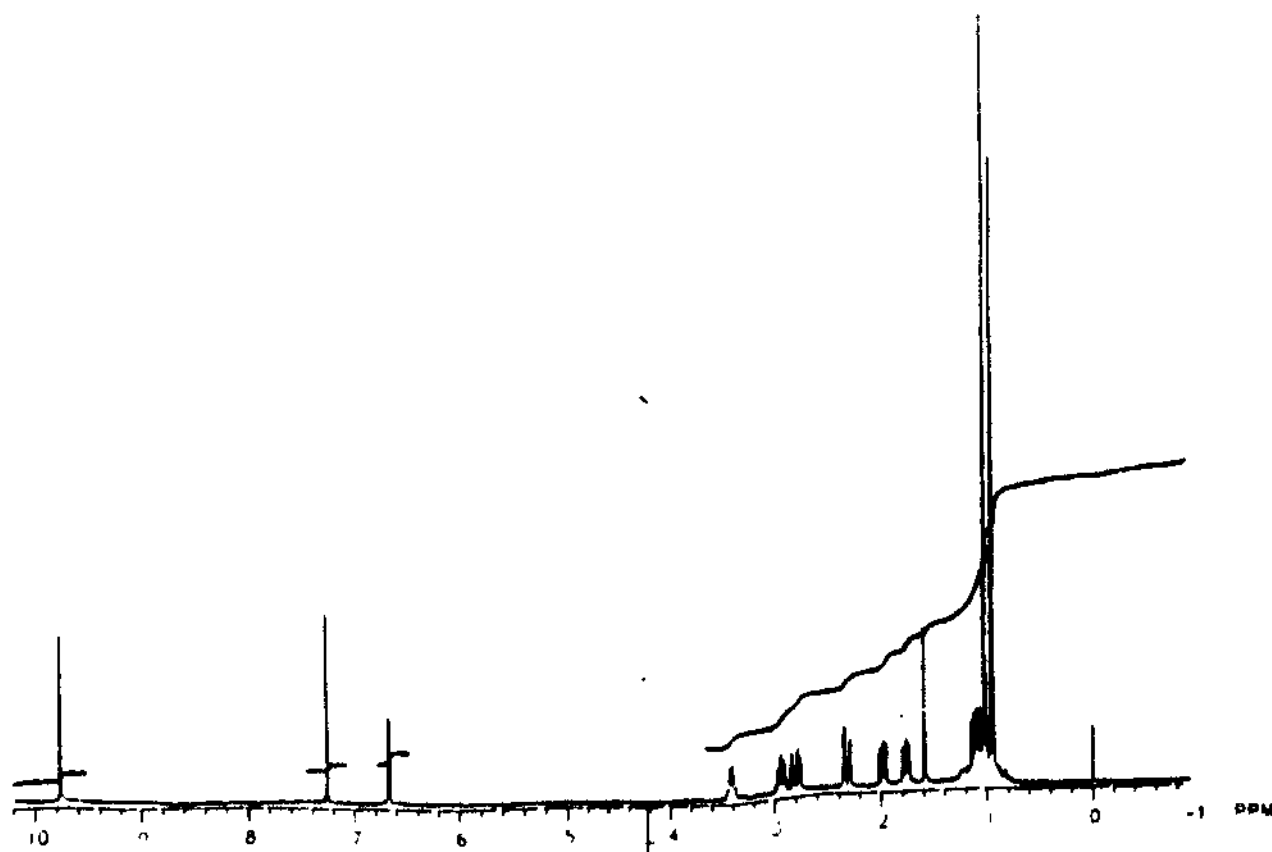
M.W.: 164.25

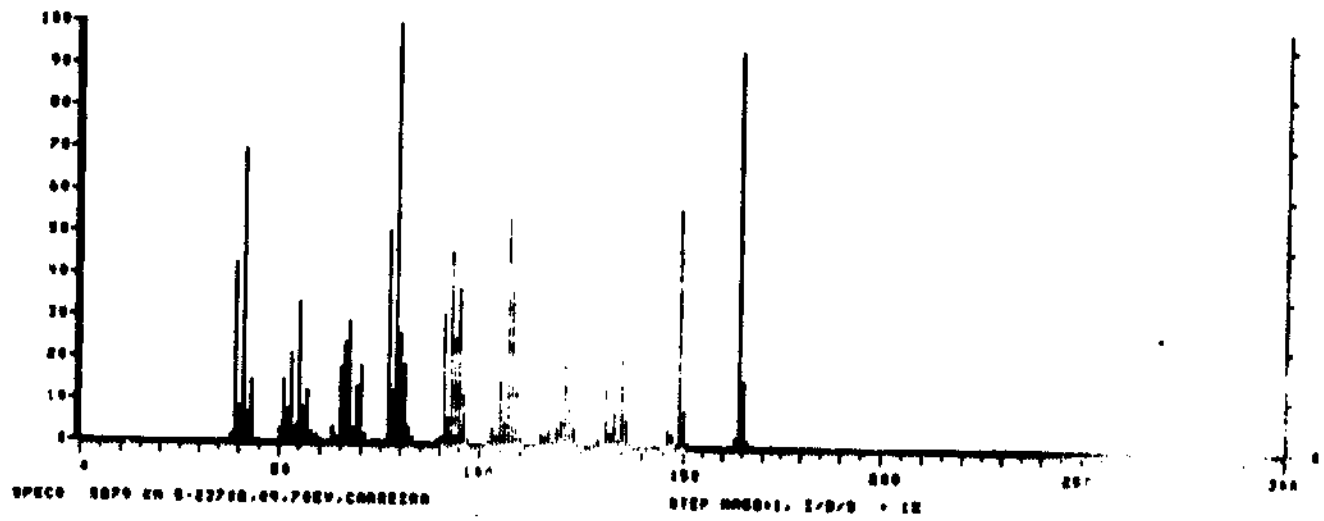
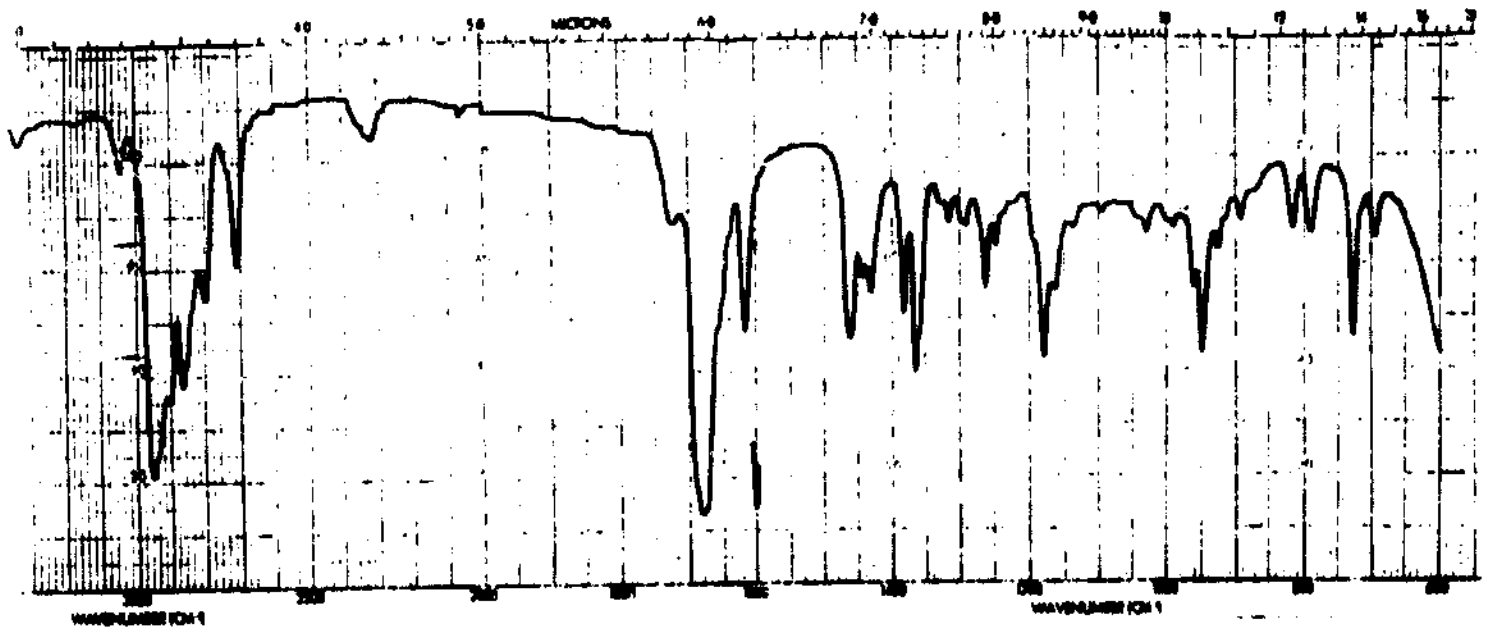
b.p.: 95°C 3 torr: Kugelrohr

<u>C<sub>11</sub>H<sub>16</sub>O</u>	calc.:	C 80.44%	H 9.82%
	found:	C 80.65%	H 10.10%

<sup>1</sup>H NMR: (360 MHz)

9.76 (s, 1H, 1H-C(1')); 6.68 (t, J=2.3Hz, 1H-C(2)); 3.46-3.39 (br m, 1H-C(6')); 2.99-2.9 (m, 2H-C(3)); 2.32 (dxdxd, J=20.0Hz, J=5.5Hz, and J=2.8Hz, 1H-C(3')); 1.99 (dxdxd, J=2.1Hz, J=8.7Hz, and J=12.8Hz, 1H-C(6)); 1.77 (dxdxd, J=2.0Hz, J=8.0Hz, and J=12.2Hz, 1H-C(6)); 1.15-1.04 (m, 2H-C(4)); 1.02 (s, 3H, 1CH<sub>3</sub>-C(5)); 0.95 (s, 3H, 1CH<sub>3</sub>-C(5)).





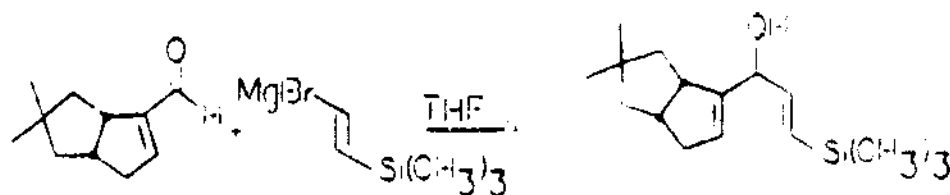
IR: (Neat)

3040w, 2950s, 2900s, 2870s, 2800m, 2710m, 1720w (sh), 1680s, 1615m,  
1460m, 1445m, 1430m, 1380m, 1365s, 1315w, 1290w (br), 1260m, 1250m,  
1180m, 1165m, 1135w, 1030w, 960m, 950s, 925m, 890w, 815w, 790w,  
730m, 695w.

M.S.: (70 ev)

165 (15.94), 164 (M<sup>+</sup>, 94.15), 149 (56.59), 135 (21.38),  
131 (21.83), 121 (19.78), 109 (12.65), 108 (39.24), 107  
(44.19), 105 (15.32), 96 (11.98), 95 (37.54), 94 (25.60),  
93 (45.69), 91 (31.06), 81 (19.27), 80 (26.50), 79 (100),  
78 (12.65), 77 (50.77), 70 (18.37), 69 (13.54), 67 (29.26),  
66 (24.06), 65 (18.13), 57 (12.50), 55 (33.95), 53 (21.16),  
51 (15.16), 43 (14.74), 41 (69.86), 39 (42.96).

Reaction of 6 with (E)-(2-bromoethyl)trimethylsilane



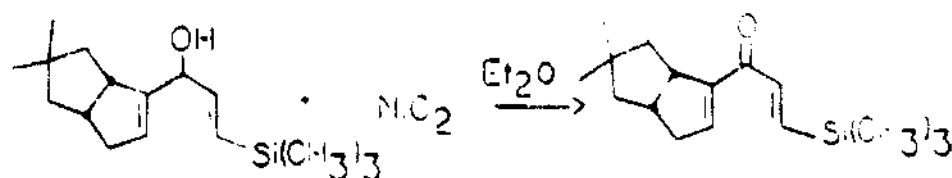
A three-necked, 15mL flask fitted with an addition funnel, magnetic stirrer, thermometer, and nitrogen inlet was charged with 53.4mg (2.20 mmol) of resublimed magnesium chips and 305 $\mu$ L of THF. A solution of 0.381g (1.83 mmol) (E)-(2-bromoethyl)trimethylsilane in 915 $\mu$ L of dry THF is added dropwise with vigorous stirring over 1.25 hr. After complete addition the yellow-green mixture is stirred for an additional two hours at room temperature.

The yellow-green suspension is cooled to -5°C using an ice/salt/water bath and a solution of 200mg (1.22 mmol) of the enal 6 in 610 $\mu$ L of dry THF is added dropwise through an addition funnel for 1 hr. The resulting colorless mixture is stirred for 15 minutes and subsequently checked by TLC.

The reaction mixture is quenched at 0°C with 2mL of a 4%  $\text{NH}_4\text{Cl}$  solution. The reaction mixture is poured into a separatory funnel and the layers separated. The aqueous phase is extracted with ether (3 x 10mL). The combined ethereal solutions are washed once with 10mL of water and brine, dried over  $\text{K}_2\text{CO}_3$  for 20 minutes, and evaporated to afford a quantitative yield of product. The crude diallyl alcohol is chromatographed on Woelm (32-63 $\mu$ ) using 7:1 hexane:ethyl acetate as the solvent system affording 502mg (94%) of product.

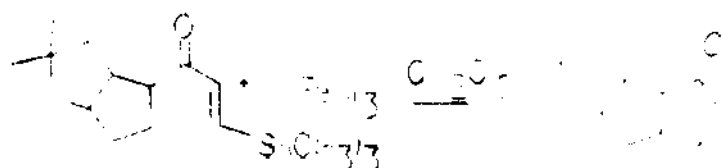


Oxidation of 7 with Nickel Peroxide



A dry three-neck 5mL flask equipped with a thermometer, mechanical stirrer, and nitrogen inlet is charged with 2.30mL of anhydrous ether and 0.263g ( $9.96 \times 10^{-4}$  moles) of the diallyl alcohol. The solution is cooled to 0°C, and, 0.784g (2.1 eq) of  $\text{NiO}_2$  is added in one portion through a powder funnel. The dark suspension is stirred at 0°C for 10 minutes and then allowed to come to room temperature. The heterogeneous mixture is allowed to react at room temperature for 2.5 hr. The contents of the reaction vessel are filtered through a Buchner funnel and the  $\text{NiO}_2$  washed thoroughly with reagent grade acetone. The filtrate is concentrated on a rotary evaporator and the residue purified by flash chromatography on Woelm (32-63 $\mu$ ) using 18:1 hexane:ethyl acetate as the solvent system affording 192mg of a pale yellow crystalline solid.

The Silicon-directed Nazarov Cyclization of 8



A 25mL flask equipped with  $\text{CaCl}_2$  drying tube and magnetic stirrer is charged with 130mg (0.445 mmol) of the dieneone in 4.95mL of 1,2-dichloroethane. To the vigorously stirred solution is added 84.4mg (1.05 eq) of  $\text{FeCl}_3$  in one portion and the reaction progress is monitored by TLC. After 2.5 hr. the reaction is judged complete and the contents of the flask poured into a separatory funnel. The dark-orange organic solution is washed repeatedly with brine until the brine wash is colorless. The brine washes are back extracted twice with 10mL of ether. The combined organic solutions are washed once with 10mL brine, dried over  $\text{MgSO}_4$ , and concentrated on a rotary evaporator. The product is immediately flashed on silica gel using 4:1 Hexane EtOAc as the solvent system to give 53.3mg (57%) of a crystalline product. GC (column A) and NMR analysis of the reaction product revealed the presence of a mixture of isomers.

Hydrogenation of 9

A 10mL flask equipped with magnetic stirrer is charged with 6.60mg of enone 9 (2.7:1 isomeric ratio by GC Column A) and 2mL of reagent grade ethyl acetate. The catalyst (0.01 eq of 5% Pd-C) is subsequently added and the resulting heterogeneous mixture stirred at room temperature at 1 atm  $H_2$  for 17 hrs. The mixture was filtered through celite, the catalyst washed with ethyl acetate and the filtrate concentrated on a rotary evaporator. GC analysis on Column A showed an isomeric ratio of 2.6:1.

Treatment of 9a with  $NaOCH_3$

A 10mL flask equipped with magnetic stirrer and nitrogen inlet is charged with the hydrogenation product and 7.65 $\mu$ L of a 0.272 M solution of  $NaOCH_3$  (0.1 eq). The resulting mixture is stirred for four hours at room temperature. GC analysis (Column A) showed an isomeric ratio of 2.6:1.

V. Summary

The silicon-directed Nazarov cyclization can be iteratively employed in the construction of linear polyquinanes. A partial synthesis of hirsutene has been accomplished which utilizes this novel synthetic transformation.

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